Infering the selective pressures acting on insertions and deletions in the great tit genome

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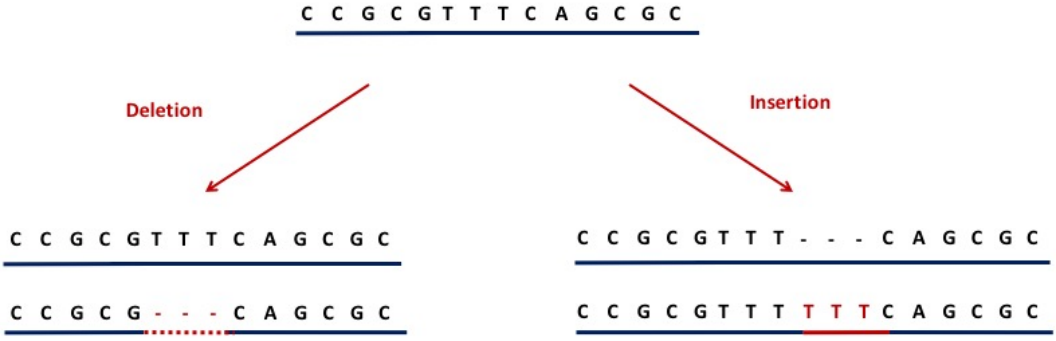
Introduction

Insertions and deletions

- short INDELs: sections of DNA $<$ 50bp that are deleted or inserted in a genome
- deletion bias in most organisms
- deletions more deleterious than insertions



INDELs often overlooked

- Disproportionately occur in repetitive sequence
- Hard to align
- Often occur in hotspots
- 1/8 as frequent as SNPs in humans

(Earl et al., 2014; Montgomery et al., 2013)

The importance of INDELs in genome evolution

- Influence genome size:
  - low deletion rate $\rightarrow$ large genomes?
  - high deletion rate $\rightarrow$ compact genomes?
  - selection on insertions to maintain minimum intron size?
- Contribute more to sequence divergence, in terms of the number of base differences, than SNPs

(Britten, 2002; Leushkin and Bazykin, 2013; Nam and Ellegren, 2012; Ometto et al., 2005; Sun et al., 2012)

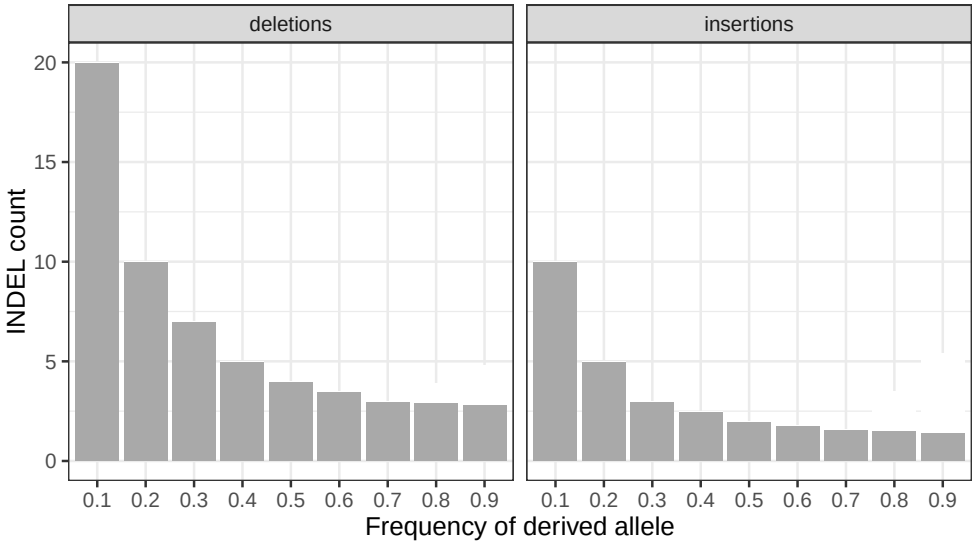
INDEL mutation

- Deletion bias in most organisms
- Polymerase slippage can explain majority of short INDEL events

INDEL selection

- Deletions
  - lower mean allele frequency
  - more deleterious
  - two breakpoints
- Insertions may be favoured:
  - elevated fixation probability
  - biased gene conversion
  - minimum intron size
  - polarisation error

Importance of polarisation error



(see Hernandez et al., 2007)

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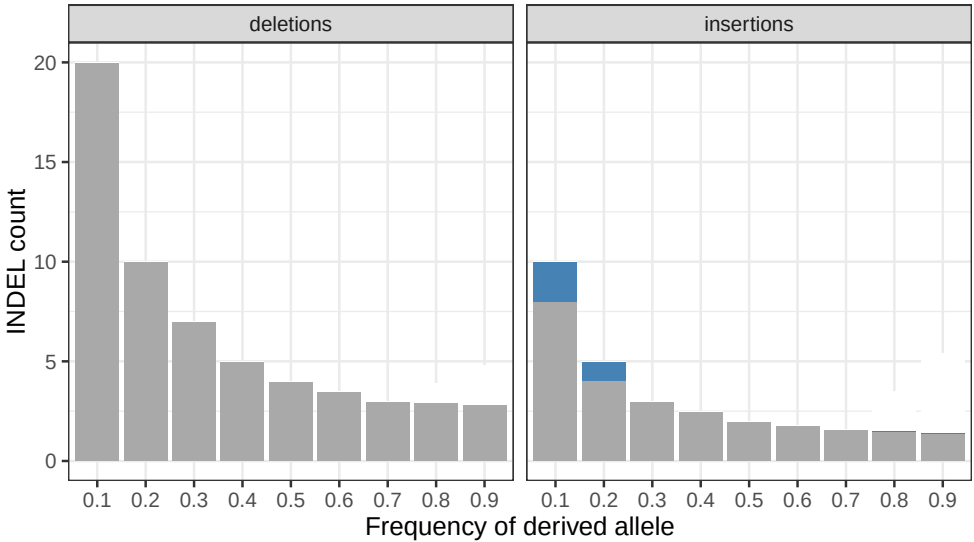

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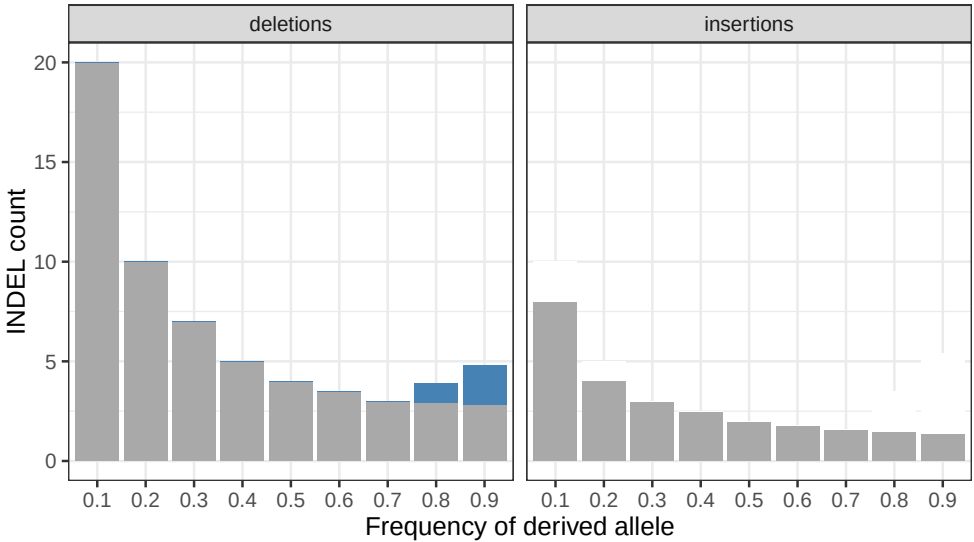

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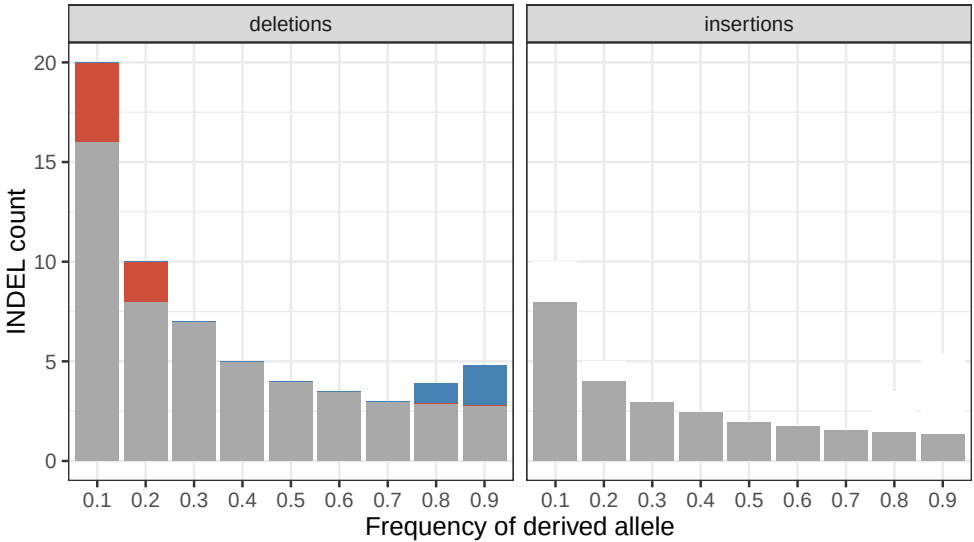

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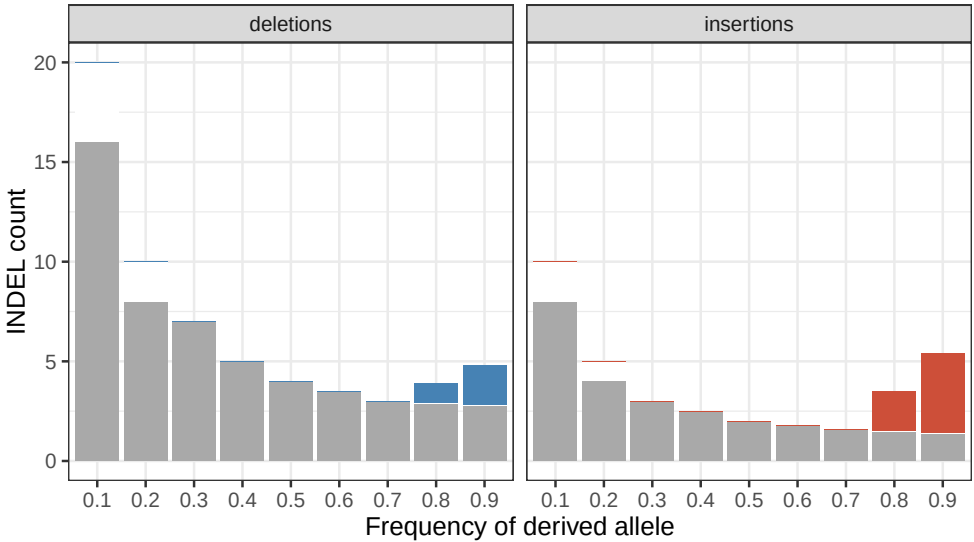

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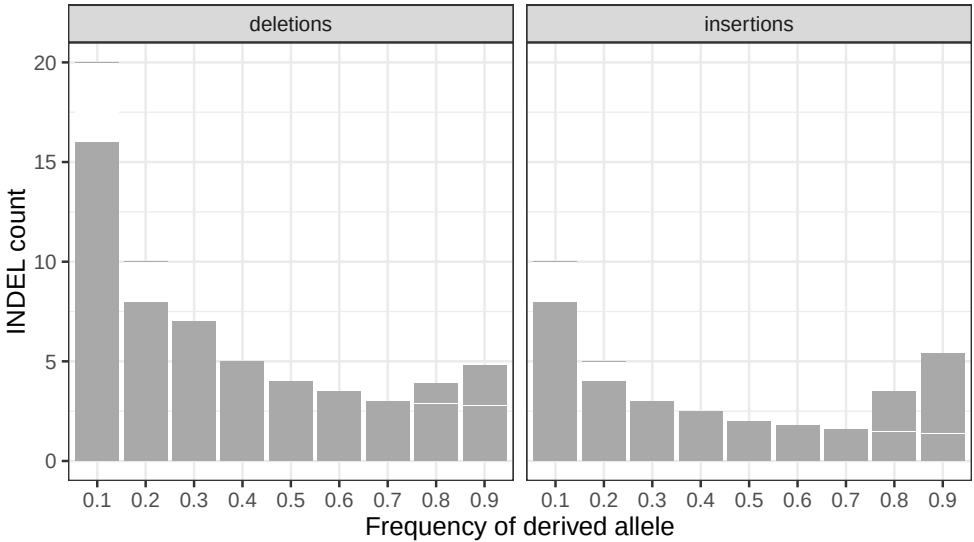


(see Hernandez et al., 2007)

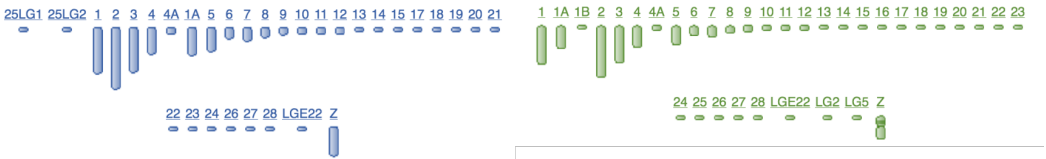
Aims

Quantify how natural selection shapes INDEL diversity in the great tit (*Parus major*)

1. within coding regions
2. in non-coding regions

Advantages of an avian system

- Conserved karyotype and synteny - good for alignments
- Genomes consist of few large macrochromosomes and many small microchromosomes
- Results in a highly dynamic recombination landscape - power to associations with recombination

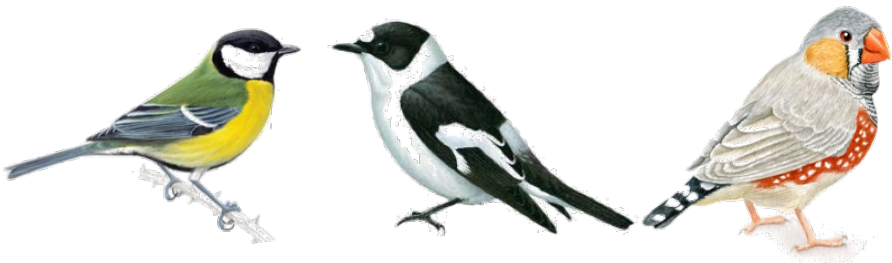


(van Oers et al., 2014; Stapley et al., 2008)

Data

Sample and pipeline

- 10 european great tit males (Corcoran et al., 2017)
- high coverage (44x)
- variant calling with GATK
- multispecies alignment between zebra finch, flycatcher and great tit
- parsimony based polarisation



The model - ‘anavar’

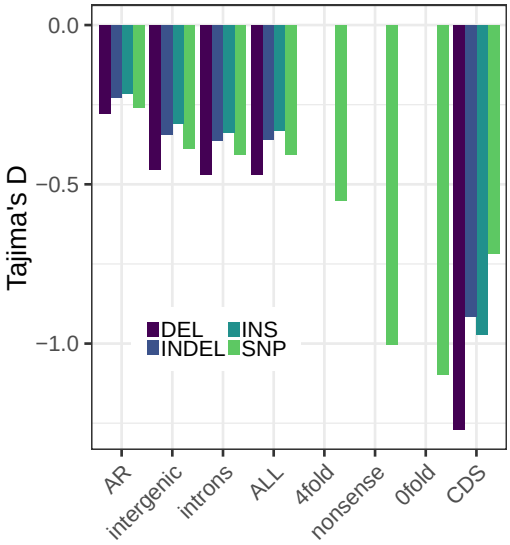
A novel maximum likelihood approach

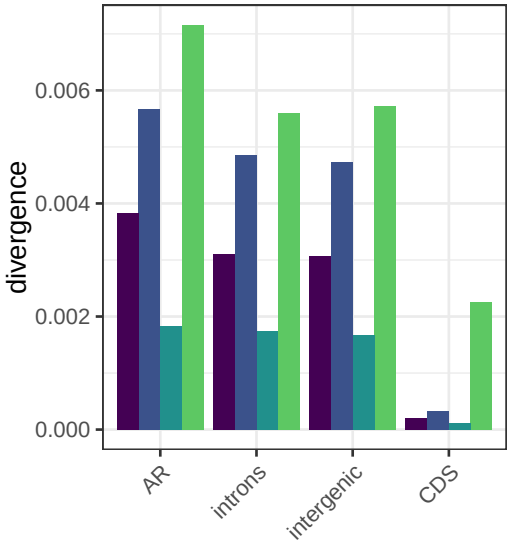
- takes the unfolded site frequency spectrum
- estimates for both insertions and deletions:
  - mutation rate ($\theta = 4N_e\mu$)
  - selection:
    - either selection coefficient ($\gamma = 4N_e s$)
    - or scale and shape paramater for distribution of fitness effects
  - polarisation error
- Controls for demography using neutral sites (Eyre-Walker et al., 2006)

(Barton and Zeng, 2018)

Dataset summary

Regional variation in purifying selection

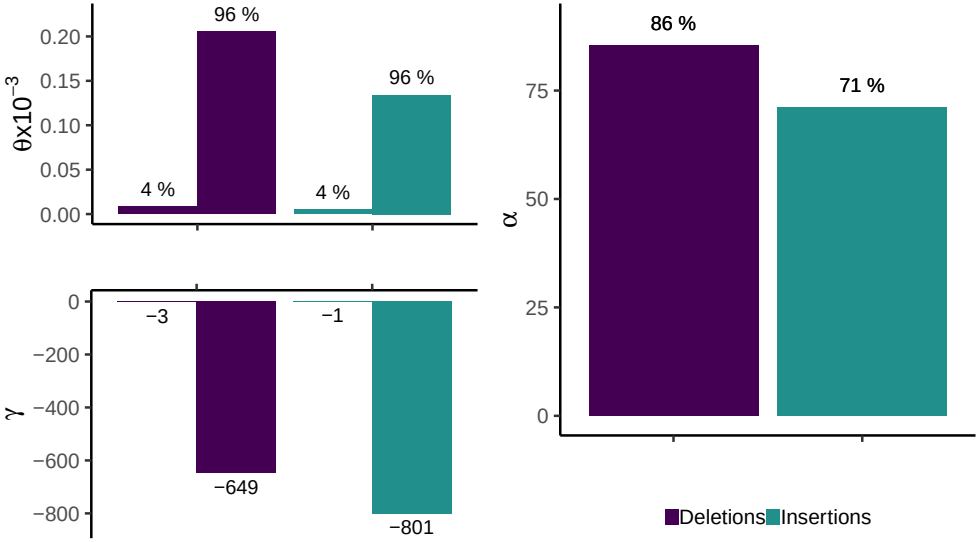




For SNPs: divergence = divergence estimate / 10

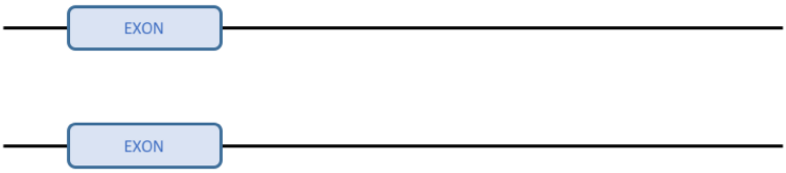
Coding INDELs

INDELs predominantly strongly deleterious



Moving away from coding regions

Approach



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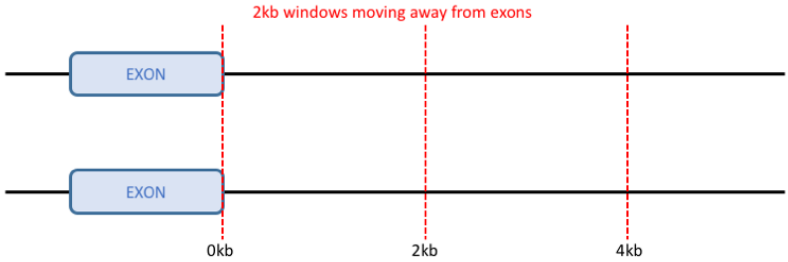

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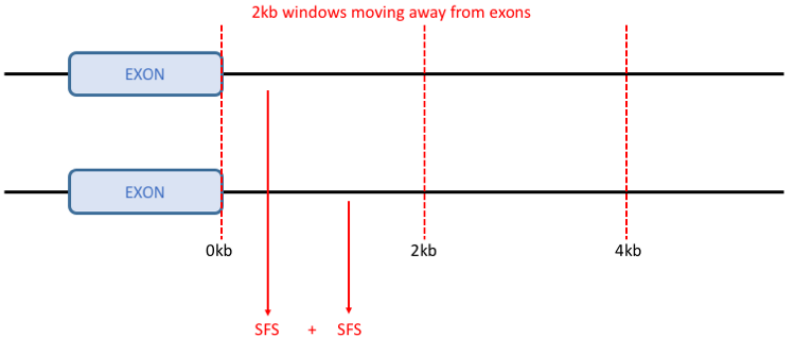
2kb windows moving away from exons
EXON
EXON
0kb
2kb
4kb
SFS
+
SFS

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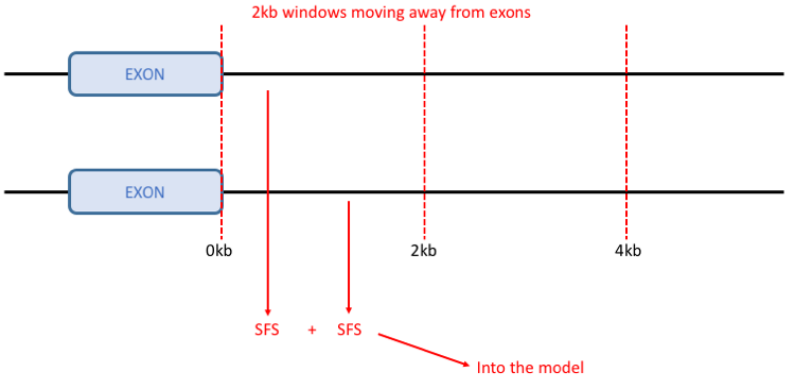
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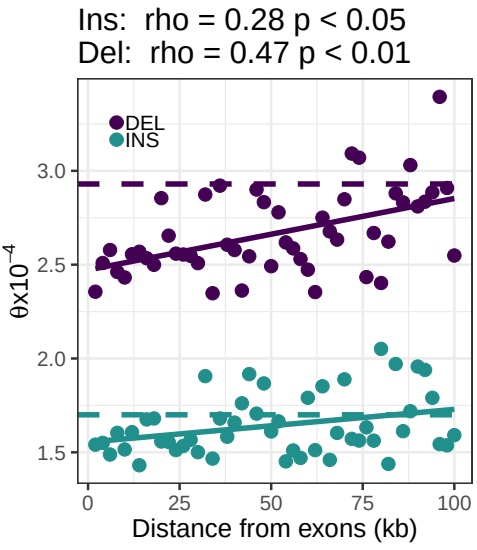
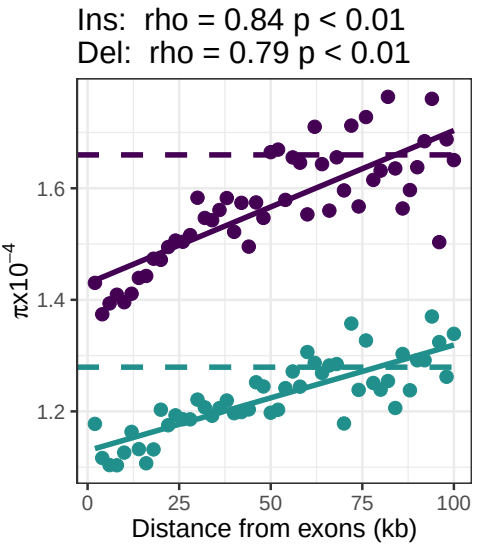
Into the model

Evidence for linked selection





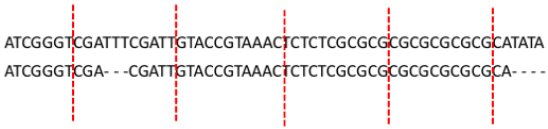
Recombination Analyses

Getting the data

ATCGGGTCGATTTCGATTGTACCGTAAACTCTCTCGCGCGCGCGCGCGCGCATATA

ATCGGGTCGA- - -CGATTGTACCGTAAACTCTCTCGCGCGCGCGCGCGCGCA- - - -

Getting the data



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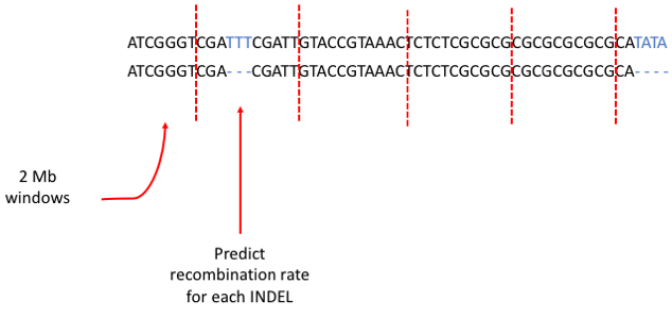
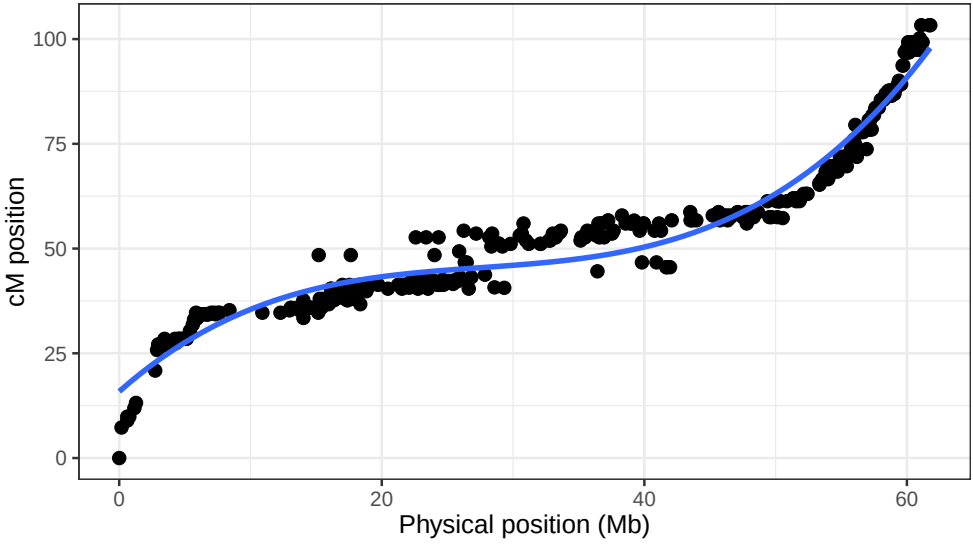


Getting the data - recombination rate



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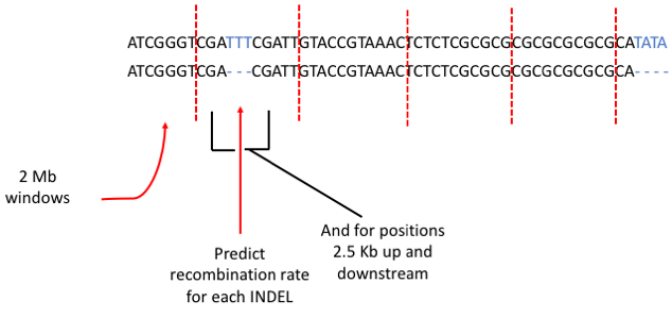

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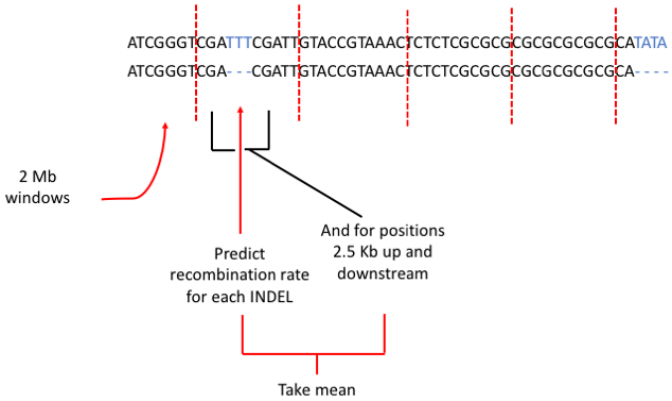

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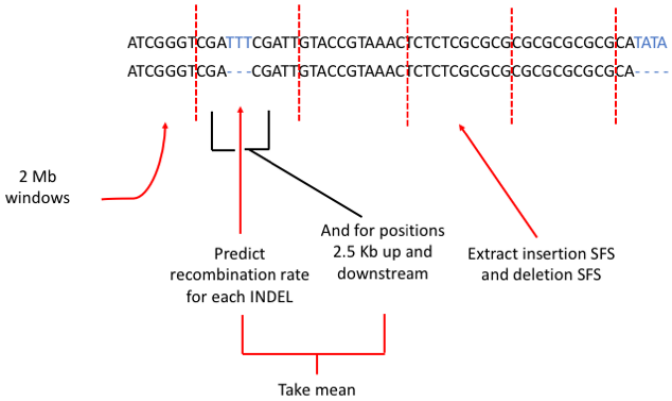

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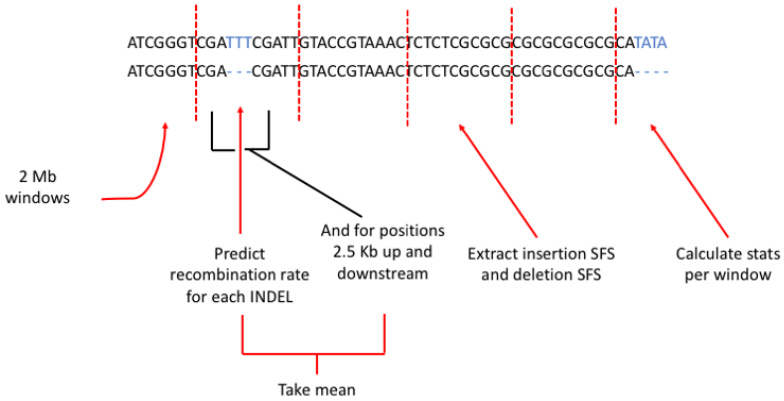
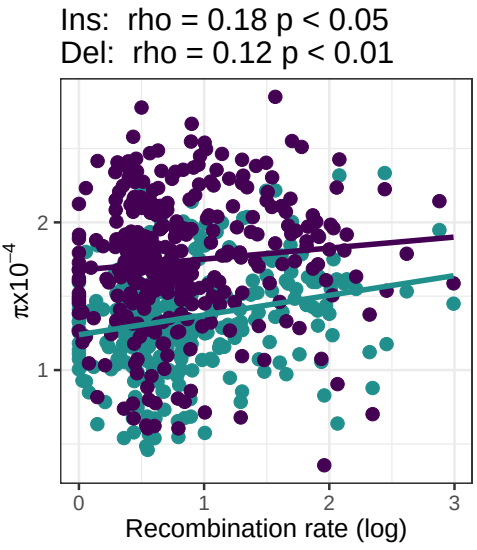
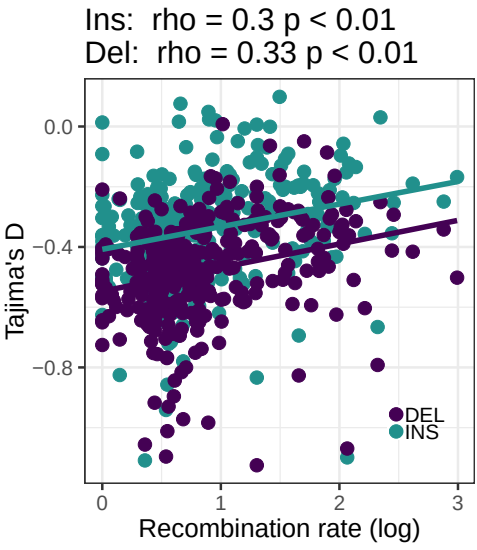


Association between diversity and recombination





Round up

Conclusion

- INDELs in genes mostly extremely deleterious - 96%
- Remainder are weakly deletrious - deletions more so
- α estimate at 71% and 86% for insertions and deletions
- Regions adjacent to exons have reduced INDEL diversity - genetic hitch-hiking
- Extends over relatively large distance 0-100kb
- Also areas of low recombination show reduced diversity

Next steps

- Intersting to investigate if reduced diversity is is due to postive selection or purrifying selection

Questions?